REMARKS

As an initial matter, applicants express their gratitude for the courtesies extended by Examiner Li and her supervisor, Anne Marie Wehbe, during an interview with applicants' representative on September 9, 2002. The following remarks reflect the content of that interview.

Receipt is acknowledged of the above-mentioned office action, where the examiner has maintained a rejection, on "non-enablement" grounds, of claims 1-38 and 65-68.

Status of the Claims

In this amendment, claims 1-3, 6, 7-15 and 18-29 have been cancelled and new claims 69-70 have been added. Support for new claims can be throughout the specification. By entry of this amendment, claims 4, 5, 16, 17, 30-38 and 65-70 will be pending in the present application.

The present amendment reduces the number of claims, simplifies the extant issues, does not necessitate a further search, and generally implements suggestions made at the September 9th interview. Accordingly, applicants respectfully request entry of the amendment and reconsideration of the present rejections in light of the following remarks.

35 U.S.C. § 112, first paragraph

All pending claims stand rejected under the first paragraph of 35 U.S.C. § 112, allegedly for lack of an enabling disclosure. Specifically, the examiner reiterated her point that the quantity of experimentation necessary to determine the parameters for achieving *in vivo* and *ex vivo* reverse gene therapy would be undue (see office action at 8).

To address the examiner's point, applicants would emphasize initially that their invention provides an approach for identifying a therapeutic gene, based on correlating the effect of a gene in one abnormality with the effect of the gene in a different abnormality to be treated. As applicants' last response noted, the inventive methodology utilizes a "yin and yang" approach, where one cellular response associated with a disease/disorder is "countered" by administering a therapeutic gene product associated with an opposite cellular response.

The amount of experimentation that the examiner characterizes as "undue" is based on the assumption that the parameters of a particular disease or disorder must be well-characterized before gene therapy will work. Importantly, knowledge of the mechanism underlying a particular disease process does not figure in implementing the methodology of the present invention. That is, the therapeutic gene is not chosen for its ability to correct a mechanistic defect presumed to underlying a pathology in abnormal tissue. Rather, the gene is selected to compensate for the "first abnormality," an identifiable symptom in the abnormal tissue. Therefore, the concept of "reverse" gene therapy can be distinguished from "traditional" gene therapy in that the therapeutic approach of the present invention does not hinge on characterizing the disease mechanism to be effective.

Accordingly, the quantity of experimentation necessary to make and use the claimed invention would not be undue. Nevertheless, in the interest of expediting prosecution, applicants cancelled claims 1-3, 6, 7-15, and 18-29, thereby qualifying claim scope in terms of treating or alleviating, with a defective HERG gene, a symptom (re-entrant atrial flutter) associated with abnormalities of a cardiac tissue. Applicants reserve the right, however, to pursue the subject matter of the cancelled claims in subsequent applications.

The examiner has asserted that "the specification does not provide a disclosure that has reduced to practice any one species of the genus for the methods of reverse gene therapy" (office action at 4). Further, the examiner contended that the additional data in applicants' supplemental response do "not provide sufficient enabling disclosure for the scope of the claims because the biophysical influence of the mutant gene has not been shown *in vivo* or in cells with [an] abnormal K^+ channel, and has not translated to any therapeutic benefit in alleviating any disease or disorder" (office action at 6).

In fact, the additional data demonstrate that Q9E-MiRP can be used in a clarithromycin-induced anti-arrhythmia regimen to slow conduction in a rapid re-entrant arrhythmia circuit. In our last response, applicants provided evidence that Q9E-MiRP not only localizes correctly to the cell membrane but also assembles properly, so as to influence the K^+ current upon administration of clarithromycin.

Moreover, the examiner has not propounded a reasonable basis for urging that the mutant HERG will not influence biophysical function *in vivo*. While the patch clamp data provided in the supplemental response are *in vitro*, they conform to the gold standard for studying electrophysiology in a cell.

Additionally, applicants would point out that their purpose was not to demonstrate "the biophysical influence of the mutant gene...on cells with [an] abnormal K^+ channel" but to show that a therapeutic gene such as HERG can counter-balance an abnormality in cells or tissues that would benefit from a lower K^+ current. As the specification describes and the supplemental data illustrate, the mutant HERG gene functions to diminish the K^+ rectifier current (Ikr) upon clarithromycin administration; hence, the gene can be used in the case of re-entrant atrial flutter, for example.

Finally, applicants have followed the examiner's suggestion (Paper No. 23), by adding claims 69 and 70. As the examiner noted during the September 9th interview, the strategy of reverse gene therapy, which the new claims reflect, is not presaged by the prior art.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

Date: October 29, 2002

By _____

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